DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 88

[NIOSH Docket 094]

World Trade Center Health Program; Petition 011--Autoimmune Diseases; Finding of Insufficient Evidence

AGENCY: Centers for Disease Control and Prevention, HHS.

ACTION: Denial of petition for addition of a health condition.

SUMMARY: On January 25, 2016, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 011) to add "autoimmune disease, lupus, and rheumatoid arthritis" to the List of WTC-Related Health Conditions (List). Upon reviewing the information provided by the petitioner, the Administrator has determined that Petition 011 is not substantially different from Petitions 007, 008, and 009, which also requested the addition of autoimmune diseases. The Administrator recently published responses to Petitions 007, 008, and 009 in the Federal Register and has determined that Petition 011 does not provide additional evidence of a causal relationship between 9/11 exposures and autoimmune diseases.

Accordingly, the Administrator finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

DATES: The Administrator of the WTC Health Program is denying this petition for the addition of a health condition as of **[INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].**

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A. WTC Health Program Statutory Authority

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Zadroga Act), Public Law 111-347, as amended by Public Law 114-113, added Title XXXIII to the Public Health Service Act (PHS Act)[1] establishing the WTC Health Program within the Department of Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders), and to eligible persons who were present in the dust or dust cloud on September 11, 2001 or who worked, resided, or attended school, childcare, or adult daycare in the New York City disaster area (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this notice mean the Director of the National Institute for Occupational Safety and Health (NIOSH) or his or her designee.

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a

[1] Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-61. Those portions of the Zadroga Act found in Titles II and III of Pub. L. 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

health condition to the List in 42 CFR 88.1. After receipt of a petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) and 42 CFR 88.17: 1. request a recommendation of the STAC; 2. publish a proposed rule in the Federal Register to add such health condition; 3. publish in the Federal Register the Administrator's determination not to publish such a proposed rule and the basis for such determination; or 4. publish in the Federal Register a determination that insufficient evidence exists to take action under 1. through 3. above. However, in accordance with 42 CFR 88.17(a)(4), the Administrator is required to consider a new petition for a previously-evaluated health condition determined not to qualify for addition to the List only if the new petition presents a new medical basis -- evidence not previously reviewed by the Administrator -- for the association between 9/11 exposures and the condition to be added.

B. Approval to Submit Document to the Office of the Federal Register

The Secretary, HHS, or her designee, the Director, Centers for Disease Control and Prevention (CDC) and

Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Thomas R. Frieden, M.D., M.P.H., Director, CDC, and Administrator, ATSDR, approved this document for publication on April 18, 2016.

C. Petition 011

On January 25, 2016, the Administrator received a petition from a responder in the WTC Health Program to add autoimmune disease, lupus, and rheumatoid arthritis to the List (Petition 011).[2] This is the fourth petition to the Administrator requesting the addition of autoimmune diseases to the List; the first three autoimmune disease petitions, Petition 007, Petition 008, and Petition 009, were each denied due to insufficient evidence as described in Federal Register notices published on June 8, 2015,[3] July 10, 2015,[4] and October 28, 2015,[5] respectively.

[2] See Petition 011. WTC Health Program: Petitions Received. http://www.cdc.gov/wtc/received.html.
[3] 80 FR 32333.
[4] 80 FR 39720.
[5] 80 FR 73667.

The current petition, Petition 011, presented eight references to support the request to add "autoimmune disease, lupus, and rheumatoid arthritis" to the List. Pursuant to WTC Health Program policy, the medical basis for a potential addition to the List may be demonstrated by reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors.[6] Of the references provided, references 1-5, 7, and an unnumbered 8th reference do not identify peer-reviewed, published studies or clinical case reports about autoimmune disease, lupus, or rheumatoid arthritis among 9/11-exposed responders and survivors. Reference 6 is a study that has already been evaluated by the Administrator in consideration of other autoimmune disease petitions.

In addition to a review of the studies presented in Petition 011, the WTC Health Program Associate Director for Science (ADS) conducted a review of the scientific literature to determine if the available scientific information has the potential to provide a basis for a

[6] See John Howard, Administrator, WTC Health Program, Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions, May 14, 2014.

decision on whether to add the condition to the List. The ADS previously conducted such a literature review for autoimmune disorders in response to Petition 007.[7] In reviewing Petition 011, the ADS conducted an additional search to update the results of the previous literature review.[8] The new literature search identified six studies published in 2015 and 2016.

In accordance with WTC Health Program policy, the ADS reviewed the eight references in Petition 011 and the six studies identified in the literature review for relevance, and then relevant studies were further reviewed for quality, and quantity.[9] The ADS review is discussed below.

Petition references 1, 2, and 3 are the websites of the S.L.E. Lupus Foundation,[10] Molly's Fund Fighting Lupus,[11] and the Johns Hopkins Lupus Center,[12] respectively. The referenced web pages discuss the development of lupus in general terms, but do not reference 9/11 exposure-related causation specifically. The Johns Hopkins web page includes references to book chapters about lupus, none of which

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[7] See 80 FR 32333 at 32334.
[8] Databases searched include: PubMed, Health & Safety Science Abstracts, Toxicology Abstracts, Toxline, Scopus, Embase, and NIOSHTIC-2.
[9] See John Howard, Administrator of the WTC Health Program, Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions, Oct. 21, 2014. http://www.cdc.gov/wtc/pdfs/WTCHP PP Adding NonCancers 21 Oct 2014.pdf.
[10] http://www.lupusny.org.
[11] http://www.mollysfund.org.
[12] http://www.hopkinslupus.org.

associate the disease with 9/11 exposure. These references are not considered relevant under the policy for adding non-cancers to the List because they are not published, peer-reviewed epidemiologic studies of autoimmune disease, lupus, and/or rheumatoid arthritis in 9/11-exposed populations and, therefore, they were not further reviewed.

Petition reference 4 is the Fire Department of New York (FDNY) EMS Retirees Association's web page on WTC Monitoring and Treatment Centers, which mentions lupus and rheumatoid arthritis and is relevant to the 9/11 population, but does not identify a published, peer-reviewed epidemiologic study or clinical case report. This reference is not considered relevant under the policy for adding non-cancers to the List because it is not a published, peer-reviewed epidemiologic study of autoimmune disease, lupus, and/or rheumatoid arthritis in 9/11-exposed populations and, therefore, it was not further reviewed.

Petition reference 5 is a 2011 Medical News Today web page that summarizes a study by Zeig-Owens, et al., "Early Assessment of Cancer Outcomes in New York City Firefighters after the 9/11 Attacks: An Observational Cohort Study," apparently for the premise that 9/11 exposures could also

trigger chronic inflammation through autoimmune disease.[13] Although the Zeig-Owens study is a published, peer-reviewed epidemiologic study relevant to the 9/11 population, it does not include any discussion of the basis for a causal association between the September 11, 2001, terrorist attacks and autoimmune disease, lupus, and/or rheumatoid arthritis. Thus, this reference is not considered relevant under the policy for adding non-cancers to the List because it is not a published, peer-reviewed epidemiologic study of autoimmune disease, lupus, and/or rheumatoid arthritis in 9/11-exposed populations and, therefore, it was not further reviewed.

Petition reference 7 is an abstract for a NIOSH-funded study titled, "Autoimmune Disease among WTCHR [WTC Health Registry] Registrants: Survey Design and Preliminary Response Rates."[14] Because the study is on-going and not yet published, it is not considered relevant under the policy for adding non-cancers to the List because it is not a published, peer-reviewed epidemiologic study of autoimmune disease, lupus, and/or rheumatoid arthritis in 9/11-exposed populations and, therefore, it was not further reviewed.

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[13] Rachel Zeig-Owens, Mayris Webber, Charles Hall, et al., Early Assessment of Cancer Outcomes in New York City Firefighters after the 9/11 Attacks: An Observational Cohort Study, The Lancet 2011;378(9794):898-905 at 904.

[14] WTC Health Program, Research Meeting Proceedings; June 17-18, 2014. www.cdc.gov/wtc/proceedings.html.

Petition reference 8 (unnumbered in the petition) is two excerpts from an HHS publication entitled, "The Future Directions of Lupus Research."[15] Neither the topic of the first excerpt, concerning environmental factors leading to the development of lupus, nor the second, concerning the role of crystalline silica in the development of lupus, addresses this disease among 9/11-exposed populations. Similar to the references discussed above, this reference is not considered relevant under the policy for adding non-cancers to the List because it is not a published, peer-reviewed epidemiologic study of autoimmune disease, lupus, and/or rheumatoid arthritis in 9/11-exposed populations and, therefore, it was not further reviewed.

The remaining petition reference, reference 6, is a 2015 study by Webber et al., titled "Nested Case-Control Study of Selected Systemic Autoimmune Diseases in World Trade Center Rescue/Recovery Workers."[16] The 2015 Webber study assessed whether 9/11-related exposure was associated with new-onset systemic autoimmune disease (including rheumatoid arthritis and systemic lupus erythematosus, or

[15] National Institutes of Health, HHS, The Future Directions of Lupus Research, Aug. 2007. http://www.niams.nih.gov/About Us/Mission and Purpose/lupus plan.pdf.
[16] Mayris Webber, William Moir, Rachel Zeig-Owens, et al., Nested Case-Control Study of Selected Systemic Autoimmune Diseases in World Trade Center Rescue/Recovery Workers, Journal of Arthritis & Rheumatology 2015;67(5):1369-1376.

SLE[17]) using a nested case-control study of male 9/11-exposed Fire Department of New York (FDNY) rescue/recovery workers. In reviewing the 2015 Webber study in consideration of Petition 007, the ADS found that the study was relevant and conducted further review for quantity and quality of evidence in the study. Ultimately, the ADS found that the study lacked information on other important confounders that could explain associations between 9/11-related exposures and systemic autoimmune diseases; in addition, there were limitations regarding the sample size, methods used to quantify exposure, and generalizability. Taken together, these limitations led the ADS to conclude that the available information did not have the potential to form the basis for a decision on whether to propose adding autoimmune diseases to the List of WTC-Related Health Conditions for Petition 007.[18]

The ADS identified six references in the literature review performed pursuant to the policy for adding non-cancer health conditions to the List. Four were found to be not relevant because they were not epidemiologic studies, therefore they were not further assessed. One study was the

[17] Systematic lupus erythematosus is the most common type of lupus. See CDC: Lupus. http://www.cdc.gov/lupus/index.htm.
[18] See 80 FR 32333 at 32334.

2015 Webber et al. study reviewed by the Administrator in consideration of Petition 007, discussed above.

The final study identified in the literature review was a 2016 epidemiologic study by Webber et al.[19] The 2016 Webber study is a follow-up to the 2015 Webber study, which looked at the association between 9/11-related exposures and systemic autoimmune diseases. The 2016 Webber study looked at the same cohort of FDNY rescue/recovery workers included in the 2015 study to estimate the incidence of systemic autoimmune diseases from September 12, 2001, through September 11, 2014, in the cohort of FDNY rescue/recovery workers. The authors also compared the FDNY incidence rates to rates from demographically similar men included in the Rochester Epidemiology Project (REP) and to other published rates, in order to measure observed FDNY cases against the number of cases expected. Because this study was found relevant, it was further reviewed and evaluated for quantity and quality to provide a sufficient basis for deciding whether to propose an addition to the List.

[19] Mayris Webber, William Moir, Cynthia Crowson, et al., Post-September 11, 2001, Incidence of Systemic Autoimmune Diseases in World Trade Center-Exposed Firefighters and Emergency Medical Service Workers, Mayo Clin Proc 2016;91(1):23-32.

In the 2016 study, Webber et al. confirmed cases of systemic autoimmune diseases in the FDNY cohort either through medical records review using the American College of Rheumatology criteria or based on self-reports deemed "probable" by two board certified rheumatologists. The study identified 97 cases of systemic autoimmune diseases among the FDNY cohort (63 medical record-confirmed cases and 34 probable self-report cases). The authors next calculated incidence for each specific autoimmune disease identified in the study among the FDNY cohort, and also calculated the incidence for all systemic autoimmune diseases combined.

The 2016 Webber study then looked to the REP comparison group to provide age- and sex-specific incidence rates during a similar time period as reviewed for the FDNY cases. Incidence rates for the REP comparison group were only available, however, for a limited subset of five autoimmune conditions: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, SLE, and scleroderma. By applying the REP incidence rates to the FDNY cohort, the study authors were able to generate age-specific expected numbers of cases for the FDNY cohort. The observed incidence rates in the FDNY cohort were then compared with the expected numbers of cases for the FDNY cohort derived

from the REP rates. Standardized ratios, which are the ratios of the observed number of cases in the FDNY cohort to the expected number of cases (based on the REP rates) were then calculated. Overall, FDNY rates for the five types of autoimmune disease compared were not significantly different from expected rates (SIR, 0.97; 95% CI, 0.77-1.21). Only SLE had a standardized incidence ratio that was statistically significantly greater among the entire FDNY cohort. Other ratios were either reduced or not statistically significant.

Limitations similar to those found in the 2015 Webber study, discussed above, were seen in the 2016 Webber study, including the lack of information on potential confounders such as family history of autoimmune disease and both work-related and recreational non-9/11-related exposures, and poor generalizability to other 9/11-exposed groups. The 2016 Webber study did not include new or additional information or controls that would avoid or mitigate the limitations found in the 2015 study. Consistent with the assessment of Petition 007,[20] the ADS disagreed with the method for measuring chronic exposure with a duration variable that did not differentiate between those with one

[20] See 80 FR 32333 at 32334.

day versus many days of exposure in a given month. Furthermore, the lack of information about occupational history and other potential confounders among the REP cohort calls into question the applicability and comparability of the rates used in the 2016 Webber study.

D. Administrator's Determination on Petition 011

The Administrator has established a policy for evaluating whether to propose the addition of non-cancer health conditions to the List of WTC-Related Health Conditions.[21] Petition 011 requested the addition of autoimmune diseases which were previously reviewed by the Administrator for Petition 007, and neither the references included in the petition nor the studies found in the literature review conducted by the ADS presented evidence of a causal association between 9/11 exposures and autoimmune diseases, lupus, and/or rheumatoid arthritis. The Administrator initially reviewed the findings presented in the 2015 Webber study in response to Petition 007, which also requested the addition of autoimmune diseases, including rheumatoid arthritis and connective tissue

[21] John Howard, Administrator of the WTC Health Program, Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions, Oct. 21, 2014. http://www.cdc.gov/wtc/pdfs/WTCHP_PP_Adding_NonCancers_21_Oct_2014.pdf.

diseases. In that review, due to limitations in the 2015 Webber study, the Administrator determined that insufficient evidence existed to take any of the following actions: propose the addition of autoimmune diseases to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.17(a)(2)(ii)); publish a determination not to publish a proposed rule in the Federal Register (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.17(a)(2)(iii)); or request a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.17(a)(2)(i)). The 2015 Webber study was also presented as evidence to support Petition 008 regarding autoimmune disorders, specifically encephalitis of the brain, as well as Petition 009 regarding the autoimmune disorder multiple sclerosis.

In reviewing the 2016 Webber study for potential support for Petition 011, the ADS concluded that similar inadequacies existed for the 2016 study as those seen in the 2015 Webber study. Taken together, the two Webber studies, while meeting the relevance threshold of being published, peer-reviewed epidemiologic studies of autoimmune disease, including lupus and rheumatoid arthritis, in 9/11-exposed populations, were found to

exhibit significant limitations and were thus insufficient to provide a potential basis for a decision on whether to propose adding the requested health conditions to the List.

Accordingly, with regard to Petition 011, the Administrator has determined that insufficient evidence exists to take further action at this time, including either proposing the addition of autoimmune diseases to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.17(a)(2)(ii)) or publishing a determination not to publish a proposed rule in the Federal Register (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.17(a)(2)(iii)). The Administrator has also determined that requesting a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.17(a)(2)(i)) is unwarranted.

For the reasons discussed above, the request made in Petition 011 to add autoimmune disease, lupus, and rheumatoid arthritis to the List of WTC-Related Health Conditions is denied.

The Administrator will continue to monitor the scientific literature for publication of the results of the ongoing WTC Health Registry study discussed above

(reference 7 in the petition) and any other studies that address autoimmune diseases among 9/11-exposed populations.

Dated: April 20, 2016.

John Howard,

Administrator, World Trade Center Health Program and Director, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

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